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Patterns of Left Ventricular Dilation During the Six Months After Myocardial Infarction

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Changes in left ventricular volume after a first myocardial infarction were studied in 50 patients. Serial radionuclide angiograms were obtained 48 h, 10 days and 1 and 6 months after infarction and left ventricular volume measured by a nongeometric method. Left ventricular dilation (≥20% increase in end-diastolic volume) occurred within 10 days of infarction in 11 patients, who had a mean volume increase of 34 ± 15% (p = 0.002 versus 48 h) at 10 days and 61 ± 43% (p = 0.01 versus 10 days) at 6 months. Ten other patients manifested left ventricular dilation between 10 days and 6 months with a lesser volume increase of 42 ± 18% by 6 months.

Among the 21 patients with ventricular dilation, progressive dilation (serial volume increases ≥20% on two or more occasions) occurred in 8 patients, who all had a large anterior infarct. Mean volume increases at 10 days and 1 and 6 months were 27 ± 20%, 49 ± 40% (p = 0.03 versus 10 days) and 79 ± 37% (p = 0.006 versus 1 month), respectively, in this group. In patients with progressive dilation, left ventricular ejection fraction decreased from 35 ± 6% at 48 h to 24 ± 10% at 1 month (p < 0.001) and 27 ± 10% (p = 0.006) at 6 months. Between 1 month and 2 years after infarction six patients died, of whom four had progressive dilation.

Severe left ventricular dilation can develop within the first 10 days after infarction and may progress during the next 6 months, with deterioration in ventricular function and a high likelihood of death.

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Left ventricular dilation and impaired ventricular function convey a poor prognosis after myocardial infarction (1–5). Dilation of the infarct zone may appear within the first few days (6,7), reflecting early infarct expansion (8). Subsequently, remodeling of the entire left ventricle may ensue with lengthening of both the infarcted and noninfarcted regions (9,10). The remodeling process may be associated with global dilation of the left ventricle and appears to represent a compensatory mechanism for maintenance of ventricular stroke volume after infarction. Ventricular dilation is most frequent in patients with a large infarct and those with persistent occlusion of the infarct-related artery (11).

An important question is whether this process of ventricular dilation eventually compensates for the impairment of ventricular function after infarction, and dilation therefore stabilizes, or whether compensation fails to occur in some patients so that dilation continues for a prolonged period. Although several studies of changes in left ventricular volume early after infarction are available (6,7,10,11), less is known regarding the long-term changes. One study (12) of changes in ventricular volume in patients given thrombolytic therapy after infarction indicated that dilation may appear late after infarction. Echocardiographic evidence indicates that slow expansion of both the infarct and noninfarct zones may continue for many months after infarction (9).

Experimental studies show that treatment with angiotensin-converting enzyme inhibitors can reduce ventricular dilation (13) and improve survival after infarction (14). Initial studies (15) in humans also indicate that similar therapy may attenuate ventricular dilation after myocardial infarction. Further clarification of the natural history of postinfarction

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left ventricular dilation in humans, therefore, is desirable to evaluate the possible benefits of such interventions.

This study prospectively examined changes in left ventricular volume during the 6 months after myocardial infarction to determine the time course of ventricular dilation. Particular attention was given to assessing the time of onset of dilation and determining whether dilation was progressive. Patients were then followed up for 2 years to compare the clinical outcome of progressive ventricular dilation with that of stabilized left ventricular volume.

Methods

Study group. Patients admitted to the coronary care unit with a first myocardial infarction were assessed for inclusion in the study. At the time of this study, thrombolytic therapy was not routinely administered in our institution and those patients who received thrombolytic therapy during clinical trials were not included in the study. The study group thus allowed a prospective study of the natural history of left ventricular volume changes after infarction. Patients with concurrent valvular or cardiomyopathic disease, atrial fibrillation or age >70 years were excluded. Patients with evidence of mitral regurgitation due to papillary muscle dysfunction were also excluded. If a radionuclide angiogram could not be performed within 48 h of infarction, the patient was excluded. The study protocol was approved by the hospital ethics and review committee and all patients gave informed consent to participate.

Study protocol. For each patient, the diagnosis of myocardial infarction was confirmed by the presence of chest pain, new Q waves or persistent ischemic T wave changes on the electrocardiogram (ECG), and a rise in plasma creatine kinase to at least twice the upper limit of normal (150 U/liter) with a significant MB fraction (>6%) on two occasions. Plasma creatine kinase was measured every 8 h to peak levels, then daily until it returned to normal. Patients with recurrent chest pain and a secondary rise in plasma creatine kinase, consistent with reinfarction, were excluded. Cardiac catheterization was performed on 33 patients (18 with anterior and 15 with inferior infarction) during the convalescent period, and contrast ventriculography in the right anterior oblique projection confirmed absence of mitral regurgitation.

Each patient's clinical course was followed at clinic visits, 1 and 6 months after infarction. During the next 2 years, patients were followed up in the clinic or by local practitioners. Information gathered from clinical records and telephone interviews with patients and local practitioners was recorded in a computerized data retrieval system. Cardiac mortality was defined as sudden death (within 1 h of cardiac symptoms) or death from reinfarction or refractory cardiac failure.

Measurement of left ventricular volume. Equilibrium radionuclide angiograms were performed within 48 h of infarction and repeated at 10 days and 1 and 6 months after infarction. The patient's erythrocytes were labeled "in vivo" with an initial intravenous injection in the right arm of 10 μg/kg body weight of stannous pyrophosphate (Mallinckrodt) followed after 10 min with 15 mCi technetium-99m pertechnetate (16). The angiogram was acquired with the use of a gamma camera with a high sensitivity slant-hole collimator (Sigma 420, Ohio Nuclear). The patient was supine and the collimator aligned in a 30° left anterior oblique position with slant holes directed caudally. Radionuclide counts were collected for 6 min, with use of a matrix size of 64 × 64 pixels with the cardiac cycle gated into 24 frames (Digital Equipment Co., Gamma II).

Immediately after scanning, a 5 ml venous blood sample was collected from the left arm. This sample was weighed and counted at 15 cm above the same collimator for 2 min to determine the count rate per milliliter of blood. All radionuclide data analysis was performed by experienced nuclear medicine technicians who were unaware of the patient's clinical status. The left ventricular blood pool at end-diastole and end-systole was defined by an edge-detection algorithim (17) with manual modification by the operator if necessary. Noncardiac radionuclide activity was measured in a background region lateral to the end-systolic blood pool.

Left ventricular volume was calculated with a nongeometric counts-based technique (18,19). The background-corrected count rate in the left ventricular blood pool at end-diastole was normalized to the count rate per milliliter of peripheral venous blood with a correction for radionuclide decay:

$$\text{LVEDVrn} = \frac{\text{left ventricular end-diastolic count rate}}{(\text{count rate/ml blood}) \times e^{0.0019251t}},$$

where LVEDVrn = radionuclide left ventricular end-diastolic volume; t = time in minutes from the midpoint of the scan to counting of the peripheral blood sample; and $e^{0.0019251t}$ = decay rate of technetium-99m activity.

The radionuclide volume measurement is less than the true left ventricular volume measurement because of tissue attenuation of the technetium-99m photon activity (20). Because this study examined changes in left ventricular volume in individual patients, correction for tissue attenuation was not employed, but each patient served as his or her own control. Each patient's initial left ventricular end-diastolic volume measurement was normalized to 100 U and subsequent volumes expressed relative to this initial volume. Normalized left ventricular stroke volume was also calculated as the product of ejection fraction and left ventricular end-diastolic volume at each study. The reproducibility of serial nongeometric radionuclide measurements of left ventricular volume has been evaluated in two previous studies (11,20), and the variation in sequential volume measurements is <20%. Accordingly, left ventricular dilation was defined as an increase in left ventricular end-diastolic vol-

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Table 1. Characteristics of Patient Groups (n = 50) According to Change in Left Ventricular Volume During the 6 Months After Infarction

	Left Ventricular Volume		
	Increase	Stable	Decrease
Age (yr)	56 ± 8	55 ± 7	56 ± 7
Men	18	17	7
Women	3	4	1
Anterior MI	12	12	5
Inferior MI	9	9	3
Peak CK (U/liter) (mean ± SD)	2,539 ± 1,468	1,741 ± 983	1,418 ± 921

MI = myocardial infarction; CK = plasma creatine kinase

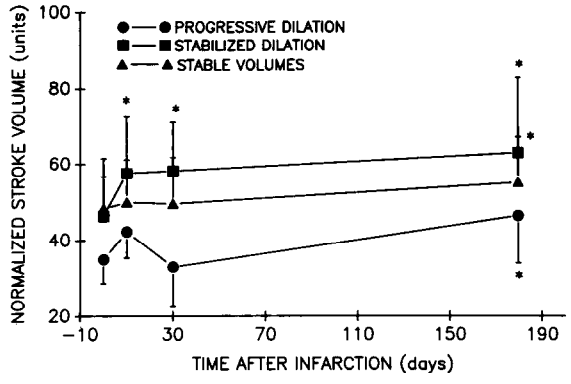


Figure 1. Time course of changes in left ventricular end-diastolic volume. Patients are grouped according to whether an increase in volume ≥20%, a decrease in volume ≥20% or a <20% change (stable) occurred during the 6 months after myocardial infarction (mean ± SD; 10 days n = 50, 30 days n = 46, 180 days n = 43).

ume of ≥20% relative to the initial volume. Progressive dilation was defined as an initial increase in volume of ≥20% with an additional increase ≥20% on a subsequent occasion. Patients with an initial volume increase ≥20% but no additional increase ≥20% on later studies were regarded as having stabilized dilation.

Statistical analysis. Patient characteristics were compared between groups by an unpaired *t* test. Serial changes in left ventricular volume and ejection fraction were compared within groups by repeated analysis of variance measures (21). The relation between change in volume and ejection fraction during the 6 months after infarction was determined by linear regression analysis. Results are expressed as mean ± SD and a p value <0.05 is regarded as significant.

Results

Patient characteristics. Fifty-three patients were admitted to the study, of whom 3 died before 10 days and had no second radionuclide angiogram. The remaining 50 patients (42 men and 8 women with a mean age of 55 ± 7 years) formed the study group. Twenty-nine patients had an anterior infarct, of whom 3 had a non-Q wave infarct, and 21 had an inferior infarct, of whom 4 had a non-Q wave infarct. Between 10 days and 1 month after infarction, 4 patients died and another 3 patients died between 1 and 6 months. All 43 survivors underwent repeat radionuclide angiography at 6 months.

Left ventricular volume (Table 1). During the 6 months after infarction, 21 patients manifested ≥20% left ventricular dilation. In contrast, 8 patients had a decrease in left ventricular volume ≥20% during the 6 months after infarction, while the remaining 21 patients had <20% change in left ventricular volume. The characteristics of the 21 patients with left ventricular dilation are compared with those of the 29 patients with stable or decreasing volume in Table 1. There were no differences in gender or age distribution between the groups. Among the 29 patients with an anterior infarct, 12 developed left ventricular dilation, compared with 9 of 21 patients with an inferior infarct. No patient with a non-Q wave infarct developed ventricular dilation. Patients with dilation had higher peak creatine kinase levels than did those without dilation, but the difference was not significant.

Early versus late left ventricular dilation. The time course of changes in left ventricular end-diastolic volume for patients who survived to 6 months is shown in Figure 1. In patients with a stable left ventricular volume during the 1st month after infarction, volume remained unchanged at 6 months. Similarly, in patients who had a decrease in left ventricular volume during the 1st month, volume also remained stable between 1 and 6 months. In contrast, the group with left ventricular dilation displayed a progressive increase in left ventricular volume of 25.5 ± 24% at 10 days, 40.8 ± 47.1% at 1 month and 51.4 ± 33% at 6 months.

Among the 21 patients developing left ventricular dilation, 11 manifested early dilation within 10 days of infarction. Nine of these patients survived to 6 months; the two who died had a large left ventricular volume increase (56% and 200%, respectively) before death. The patients with early dilation had a large initial volume increase of 34.4 ± 14.6% by 10 days (p = 0.002 versus volume on admission). The dilation progressed to a mean volume increase of 60.7 ± 42.5% at 6 months (p = 0.01 versus 10 days). Ten patients did not manifest dilation until >10 days after infarction and nine of these patients survived to 6 months. The mean volume increases in this group at 1 and 6 months were 17.4 ± 19.1% (p = 0.019 versus admission volume) and 42.1 ± 17.9% (p = 0.002 versus volume at 1 month), respectively.

Progressive versus stable dilation. Left ventricular dilation was progressive in 8 of the 21 patients who had a volume increase ≥20%. Five of these patients had early dilation within 10 days of infarction and 3 had later dilation (Fig. 2). In the seven patients with progressive dilation who survived

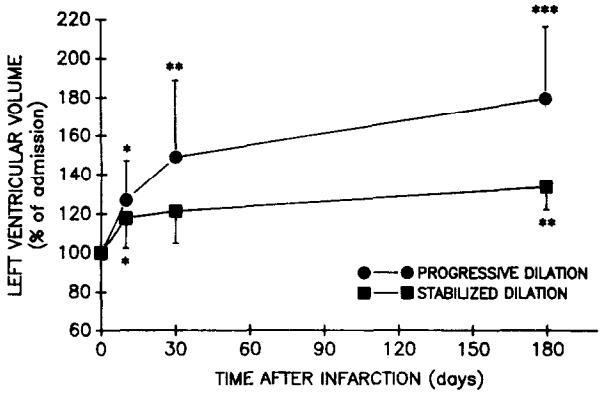


Figure 2. Comparison of left ventricular end-diastolic volume in patients with progressive ventricular dilation and those with stabilized dilation. Data are shown for the 7 patients with progressive dilation and 11 with stabilized dilation who survived for 6 months (mean ± SD; *p < 0.02 versus admission volume; **p < 0.05 versus volume at 10 days; ***p < 0.03 versus volume at 30 days).

6 months, the mean volume increase at 10 days was 26.9 ± 20% (p = 0.011 versus admission volume), increasing to 79.4 ± 37% at 6 months (p = 0.006 versus volume at 1 month). Not shown in Figure 2 is one patient who had an increase in left ventricular end-diastolic volume of 93% at 10 days and 200% at 1 month and who died before 6 months.

The other 13 patients did not meet the criteria for progressive dilation and this group displayed smaller changes in volume. In this group with stabilized dilation, 11 patients survived to 6 months, having volume increases of 17.8 ± 15.6% at 10 days, 21.4 ± 16.3% at 1 month (p = NS versus volume at 10 days) and 33.5 ± 11.5% at 6 months (p = 0.03 versus volume at 10 days) (Fig. 2). The two patients who died before 6 months had the greatest dilation in this group (volume increases of 56% and 41%, respectively, during the 1st month after infarction). All eight patients with progressive dilation had an anterior infarct and had higher peak creatine kinase levels (3,737 ± 1,162 U/liter) than did patients with stabilized dilation (2,742 ± 1,770 U/liter (p = NS).

Left ventricular ejection fraction. The patients who had a stable left ventricular volume had an admission ejection fraction of 47.8 ± 7.5%, which increased to 54.4 ± 8.9% (p = 0.029) by 6 months (Fig. 3, top panel). Similarly, patients who had a decrease in volume had an increase in ejection fraction from 47.1 ± 6.9% at admission to 54.4 ± 7.5% (p = 0.025) at 6 months after infarction. Among patients with stable dilation, left ventricular ejection fraction was unchanged from 46.3 ± 15.2% at admission to 46.0 ± 14.2% at 6 months (Fig. 3, bottom panel). In contrast, the patients with progressive dilation had the lowest admission ejection fraction (35.0 ± 6.4%), which decreased further by 1 month (23.7 ± 10.2%, p < 0.001) and 6 months (26.9 ± 9.7%, p = 0.006 versus admission value). Ejection fraction at 6 months

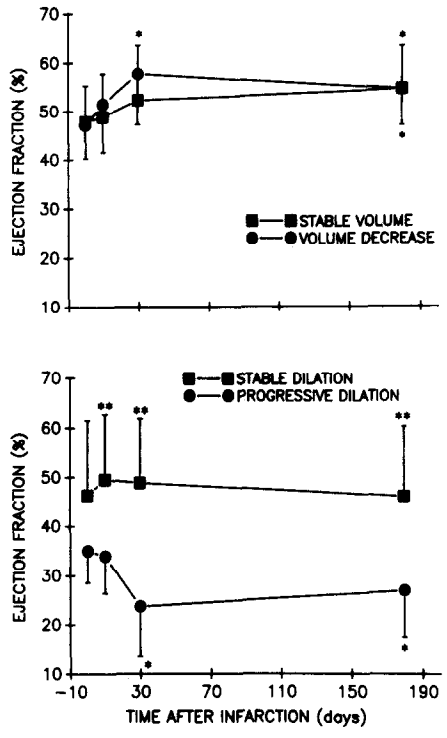
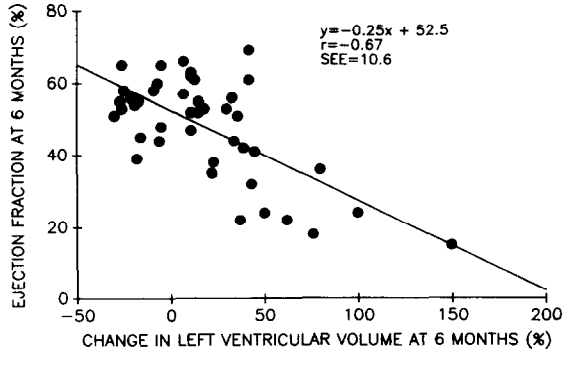


Figure 3. Ejection fraction after myocardial infarction. **Top panel**, Changes in left ventricular ejection fraction in patients with stable (n = 17) or decreasing (n = 8) ventricular volume during the 6 months after infarction (mean ± SD, *p < 0.05 versus admission value). **Bottom panel**, Comparison of ejection fraction in patients with left ventricular dilation according to whether dilation is progressive (n = 7) or stabilized (n = 11) (mean ± SD, *p < 0.01 versus admission value; **p < 0.05 versus progressive dilation).

inversely reflected changes in left ventricular volume (Fig. 4).

Stroke volume and heart rate. Changes in normalized left ventricular stroke volume are compared between patients with stable ventricular volume and those with ventricular dilation in Figure 5. Among those with stable left ventricular

Figure 4. Inverse relation between left ventricular volume change and ejection fraction in 43 patients at 6 months after infarction.



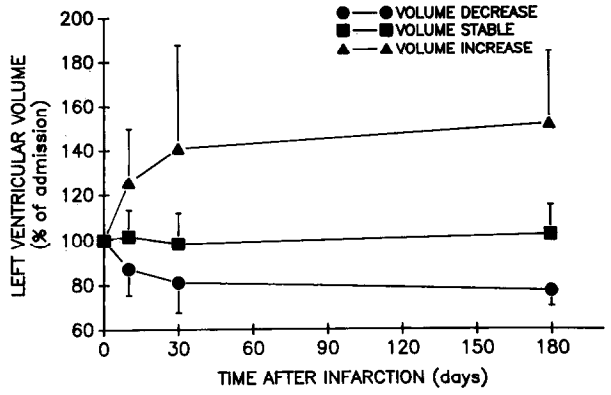


Figure 5. Comparison of normalized left ventricular stroke volume in patients with progressive ventricular dilation, those with stabilized dilation and those without dilation in the 6 months after infarction (mean ± SD, *p < 0.05 versus admission value).

end-diastolic volume, stroke volume increased from 47.8 ± 7.5 U at admission to 55.4 ± 11.7 U at 6 months ($p = 0.048$). Heart rate at admission (76 ± 12 beats/min) was unchanged at 6 months (72 ± 14 beats/min). Similarly, in those patients with dilation and subsequent stabilization of ventricular volume, stroke volume increased from 45.3 ± 13.7 U at admission to 59.6 ± 20 U at 6 months ($p < 0.01$) and heart rate was (72 ± 11 beats/min) at admission and (75 ± 13 beats/min) at 6 months. In contrast, patients with progressive dilation had the lowest admission stroke volume (33.1 ± 7.9 U), which increased to 46.4 ± 11.5 U at 6 months ($p < 0.01$), but remained less than the stroke volume of patients with stable left ventricular volumes or stabilized dilation. This group had a decrease in heart rate between admission (93 ± 12 beats/min) and 6 months (73 ± 15 beats/min, $p < 0.05$). There were no differences in mean arterial pressure between patients with left ventricular dilation and those with stable ventricular volumes.

Clinical course. No patients were lost to follow-up during the 2 years after infarction. Four of the 50 patients died between 10 days and 1 month, each of whom had a large anterior infarct and severe cardiac failure. One of these patients had an increase in left ventricular end-diastolic volume of 56% by 10 days and died at 3 weeks. The other three patients had <20% change in volume by 10 days but died of ventricular fibrillation or cardiogenic shock at 12 to 15 days.

Subsequently, three patients died between 1 and 6 months, of whom two had left ventricular dilation (including one with progressive dilation). One patient had a volume increase of 200% and developed left bundle branch block, whereas another had a volume increase of 41% before death. The remaining patient died suddenly at 6 weeks, having a volume increase of only 13%. Three additional patients died between 6 months and 2 years after infarction. Each of these patients had developed progressive left ventricular dilation with volume increases of 62%, 76% and 150% at 6 months after infarction. Therefore, of 10 patients who died during the 2 years after infarction, 6 had left ventricular dilation. Among the eight patients with progressive ventricular dilation, four died within 2 years of infarction.

Two patients were diagnosed as having left ventricular aneurysms by 6 months on the basis of ancillary investigations including echocardiography and contrast ventriculography. Both of these patients were in the progressive dilation group. Three patients with progressive left ventricular dilation required antiarrhythmic therapy for recurrent ventricular tachycardia after hospital discharge, of whom two later died. Among the eight patients with progressive dilation, seven required diuretic therapy for clinical cardiac failure, compared with only two of the patients with stabilized dilation. Three patients with progressive dilation also received treatment with angiotensin-converting enzyme inhibitors between 1 and 6 months after infarction. In contrast, none of the patients with stable or decreasing volumes manifested cardiac failure and none required diuretics or angiotensin-converting enzyme inhibitors. There was no difference in nitrate usage between patients with and without dilation. None of the patients who had progressive dilation received a beta-adrenergic blocking agent or calcium channel antagonists. Coronary revascularization (angioplasty or saphenous vein grafting) was performed within 6 months of infarction in three patients with and four patients without dilation.

Discussion

This study shows that severe global left ventricular dilation can occur within 10 days of myocardial infarction, and approximately 40% of infarct survivors will develop ventricular dilation within 6 months of infarction. In patients developing ventricular dilation, nearly 40% have progressive dilation. This progressive dilation is associated with continuing deterioration in left ventricular function and increased two-year mortality. In contrast, patients with dilation that stabilizes during the 6 months after infarction have a better clinical outcome.

Initiation of ventricular dilation. Several factors may contribute to changes in left ventricular volume after infarction, including infarct size, infarct expansion, persistent occlusion of the infarct-related artery and myocardial dysfunction due to reversible ischemia. This study and others (6,11) have shown that ventricular volume may decrease and ejection fraction increase during the weeks after infarction in some patients. This improvement probably reflects return of contractility to postischemic myocardium, a possibility supported by the relation between patent infarct-related arteries and later improvement in ventricular function (11,22,23).

The major initial volume increase observed in patients with early dilation is most likely due to lengthening of the

infarct region. The greatest risk of infarct expansion, with myocyte slippage and lengthening of the infarct segment, occurs between 3 and 10 days after infarction (8,24,25). All the patients with early dilation had a large, Q wave infarct, which is a known predisposing factor for infarct expansion. Persistent occlusion of the infarct-related artery is associated with ventricular dilation (11) and aneurysm formation (22). Such persistent occlusion may result in a larger infarct and transmural necrosis with increased risk of infarct expansion.

Mechanism of continuing dilation. In contrast to early dilation, which appears to be primarily due to lengthening of the infarct region, studies of experimental infarction (24–26) have shown that later dilation of the left ventricular cavity is associated with lengthening of both the infarcted and noninfarcted segments. Echocardiographic studies (9,10) in humans have also documented dilation of the noninfarcted region during the convalescent phase of infarction. Several studies (10,27) have indicated that ventricular wall stress is increased in both infarcted and noninfarcted regions as a result of such dilation. This increased wall stress can result in eccentric hypertrophy of the noninfarcted myocardium (28–30). These changes in left ventricular volume and wall thickness appear to represent a compensatory mechanism to maintain cardiac output after infarction (10).

The changes in left ventricular volume documented in the present study between 10 days and 6 months after infarction are consistent with this remodeling hypothesis. Thus, patients who developed left ventricular dilation had a lower initial ejection fraction and left ventricular stroke volume than did those with a stable ventricular volume. The subsequent left ventricular dilation was then associated with a restoration of left ventricular stroke volume. An important finding, however, is the difference between those patients in whom dilation stabilizes and those in whom it progresses. Patients with stabilized dilation had a return of stroke volume to the same levels as those of patients without dilation. Thus, the remodeling process in these patients appears to have compensated for the contractile impairment due to the infarct. Only mild dilation appeared to be required for compensation of stroke volume in this group.

In contrast, patients with progressive dilation have a decrease in ejection fraction and their stroke volume does not catch up with that of other postinfarction patients. Despite severe left ventricular dilation, and presumably extensive ventricular remodeling, these patients remain uncompensated. It is uncertain why compensation fails to occur in these patients, but possible mechanisms include an infarct region that is simply too large for remodeling to restore favorable ventricular geometry, or a rate of cavity dilation that exceeds the rate of eccentric myocardial hypertrophy, resulting in reduced systolic tension development. Another factor may be late deterioration in contractility of the remaining hypertrophied, noninfarcted myocardium (29,30).

Ventricular dilation and prognosis: role of therapy. The adverse effect of cardiac enlargement was demonstrated in early studies of postinfarction prognosis. More recently, left ventricular dilation has been shown to confer an added risk of late sudden death in patients with impaired left ventricular function (5). The present study, although limited in size, does suggest that it is the patient with progressive dilation who is at greatest risk of late death after infarction. The high mortality and morbidity associated with left ventricular dilation after infarction indicate a need to identify these patients. Our study shows that patients at risk for developing severe dilation, such as those with a large anterior infarct, will frequently manifest early significant dilation that can be detected by echocardiography or radionuclide angiography during the hospitalization period.

In view of the relation between occlusion of the infarct-related artery and ventricular dilation (11,15), thrombolytic therapy may decrease the risk of ventricular dilation by reducing infarct size or preserving a rim of epicardium and reducing infarct expansion. Although experimental studies (31) indicate a beneficial effect of thrombolysis on infarct expansion, one recent study (12) found no difference in late left ventricular volume between patients with successful and unsuccessful thrombolysis. Studies (15) with the angiotensin-converting enzyme inhibitor, captopril, also offer promise of attenuation of ventricular dilation after infarction. The patterns of ventricular dilation documented in this study offer a reference against which the benefit or lack of benefit of future therapeutic measures could be evaluated.

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